PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 286336.160WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/011919	International filing date *(day/month/year)* 19 April 2004 (19.04.2004)	Priority date *(day/month/year)* 18 April 2003 (18.04.2003)]
International Patent Classification (IPC) or national classification and IPC [7] A01N 65/00, C12N 5/00, 5/08, C12P 21/02, A61K 38/00, A61M 5/00		
Applicant NORWOOD IMMUNOLOGY, LTD.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 04 November 2005 (04.11.2005)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Simin Baharlou
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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HALE AND DORR LLP
60 STATE STREET
BOSTON, MA 02109

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference 286336.160WO	Date of mailing (*day/month/year*) 04 JAN 2005 FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/11919	19 April 2004 (19.04.2004)	03 June 2003 (03.06.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A01N 65/00; C12N 5/00, 08; C12P 21/02; A61K 38/00; A61M 5/00 and US Cl.: 424/93.7; 435/69.5, 325, 372; 514/12; 604/4.01, 7

Applicant

NORWOOD IMMUNOLOGY, LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Q. Janice Li Telephone No. 703-308-0196

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/11919

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/11919

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 7 and 22

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 7 and 22 are so unclear that no meaningful opinion could be formed *(specify)*:

Claim 7 recites ""the treatment of the disease". There is insufficient antecedent basis for the limitation in the claim.
Claim 22 depends from claim 120, there is no claim 120 in the application.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/11919

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 7 and 22

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 7 and 22 are so unclear that no meaningful opinion could be formed *(specify)*:

Claim 7 recites ""the treatment of the disease". There is insufficient antecedent basis for the limitation in the claim.
Claim 22 depends from claim 120, there is no claim 120 in the application.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/11919

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 5, 14, 23	YES
	Claims 1-4, 6, 8-13, 15-21, 24-27	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-6, 8-21, 23-27	NO
Industrial applicability (IA)	Claims 1-6, 8-21, 23-27	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet
Claims 1-6, 8-21, 23-27 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/11919

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1-4, 6, 8-13, 15, 16, 18-20, 24, 26, and 27 lack novelty under PCT Article 33(2) as being anticipated by Kojima et al.

Kojima et al disclose a method comprises administering an immunosuppressive agent such as cyclosporine and danazol (anti-estrogen) along with bone marrow transplantation (stem and progenitor cell from donor) and cytokine G-CSF, which lead to the engraftment of the donor cells. It is noted since the immunosuppressive agent would at least in part ablate immune cells, and danazol will disrupt the sex steroid-mediated signaling in the patient, thus the process taught by Kojima et al meet claim limitation. Accordingly, Kojima et al anticipated the instant claims.

Claims 14 and 23 lack an inventive step under PCT Article 33(3) as being obvious over Kojima et al as applied to claims 1-4, 6, 8-13, 15, 16, 18-20, 24, 26, and 27 above, further in view of Mardiney III et al.

Kojima et al do not teach using SCF as conditioning cytokine for the bone marrow transplantation.
Mardiney III et al supplemented Kojima et al by establishing that it is well known in the art numerous cytokines such as SCF could be used to enhance the therapeutic effect of BMT. Accordingly, it would have been obvious for the ordinary skilled in the art to include the SCF in the treatment procedure with a reasonable expectation of success. Thus the claimed invention is prima facie obvious in the absence of evidence to the contrary.

Kojima et al do not teach using anti-estrogen drugs other than danazol, however, they are well known in the art, would have been obvious to use in place of danazol.

Claims 1-4, 6, 8-12, 16, 18-21, 26, and 27 lack novelty under PCT Article 33(2) as being anticipated by Ghalie et al.

Ghalie et al disclose a method comprises administering leuprolide before or at the time of bone marrow transplantation (stem and progenitor cell from donor), which is preceded by total-body irradiation and cyclophosphamide therapy, and the BMT leads to the engraftment of the donor cells. It is noted that the patients have a median age of 26, thus, the thymus is atrophic, and the irradiation and the immunosuppressive agent would cause thymus atrophy otherwise, thus the pre-BMT treatment would at least in part ablate immune cells, and leuprolide will disrupt the sex steroid-mediated signaling in the patient, thus the process taught by Ghalie et al meet claim limitation. Accordingly, Ghalie et al anticipated the instant claims.

Claims 1-4, 6, 8-12, 16, 17, 26, and 27 lack novelty under PCT Article 33(2) as being anticipated by Masera et al.

Masera et al disclose a method comprises conducting orchiectomy before or at the time of bone marrow transplantation (stem and progenitor cell from donor), which is preceded by total-body irradiation and immunosuppressant therapy, and the BMT leads to the

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

engraftment of the donor cells. It is noted that the irradiation and the immunosuppressive agent would cause thymus atrophy, thus the pre-BMT treatment would at least in part ablate immune cells, and orchiectomy will surgically disrupt the sex steroid-mediated signaling in the patient, thus the process taught by Masera et al meet claim limitation. Accordingly, Masera et al anticipated the instant claims.

Claims 1-4, 6, 8-12, 16, 18-20, 25, 26, and 27 lack novelty under PCT Article 33(2) as being anticipated by Vogelsang et al.

Vogelsang et al disclose a method comprises administering aminoglutethimide and structurally similar chemical thalidomide before or at the time of bone marrow transplantation (stem and progenitor cell from donor), which is preceded by total-body irradiation and cyclosporine therapy, and the BMT leads to the engraftment of the donor cells. It is noted that the rats are at least 12 weeks old, thus, the thymus is atrophic, and the irradiation and the immunosuppressive agent would cause thymus atrophy otherwise, thus the pre-BMT treatment would at least in part ablate immune cells, and aminoglutethimide will disrupt the sex steroid-mediated signaling in the rats, thus the process taught by Vogelsang et al meet claim limitation. Accordingly, Vogelsang et al anticipated the instant claims.